mRNA Technology: What It Might Mean for Future Vaccines

AVAC
Global Health Advocacy, Access & Equity

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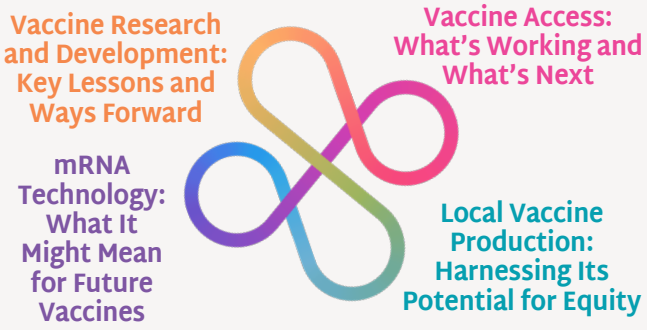
Ensuring equitable access to safe, effective and affordable vaccines involves advocacy across multiple areas. This issue brief on mRNA technology covers what it is, how it works, current knowledge gaps and ideas for advocacy to harness its potential. It is one of a series of four issue briefs, which provide a roadmap for advocacy to advance the development of essential vaccines for HIV, COVID-19, tuberculosis, and other global public health threats, and approaches to ensure equitable access to these life-saving vaccines. Additional topics cover the research and development (R&D) process, the need for local vaccine production, and issues around global access.

FROM THE LAB TO THE JAB

A series of advocate's guides



This is one in a series of four advocate's guides highlighting key advocacy issues to ensure equitable access to safe, effective, and affordable vaccines. All four briefs can be found at avac.org/FromLabToJab

Key Points

- The SARS-CoV-2 pandemic occurred just as scientists, building on decades of research, were ready to produce mRNA vaccines. mRNA-based vaccines are simpler, faster, and less expensive to produce than other types of vaccines.
- Currently, mRNA-based vaccines are being studied for cancer, HIV, influenza, tuberculosis and many other uses.
- While mRNA technology offers great promise for expanding local production of, and equitable access to, vaccines, questions remain about adverse events (AE), dosing, durability, and whether the requirement for a cold chain can be modified.

What are Ribonucleic Acid (RNA) and Messenger RNA (mRNA)?

RNA is found in all living cells. The body uses it to code, decode, regulate, and express genes. One type of RNA, called mRNA, is made in the cell's nucleus. It carries genetic instructions for making a specific viral protein to ribosomes, which translate these instructions to enable production of viral proteins.

Development of mRNA-Based COVID-19 Vaccines

SARS-CoV-2 emerged just as scientists became ready to use mRNA technology and lipid nanoparticles, which they had already been studying for decades. mRNA was discovered in the early 1960s. Scientists saw its potential for use in an HIV vaccine, since mRNA could deliver genetic instructions for creating a viral antigen or protein into cells and trigger immune responses, without using parts of an actual virus, or a weakened or inactivated virus. But the body breaks mRNA down rapidly, before it can deliver its instructions to cells. To protect it, scientists wrapped the mRNA in tiny bubbles of fat, called lipid nanoparticles. However, they faced another challenge: the body recognized the mRNA as a foreign substance, which triggered inflammatory responses.

Drs. Katalin Karikó and Drew Weissman, who were working on an mRNA-based HIV vaccine, realized that the mRNA they were using needed to be modified. They altered it to nearly eliminate any inflammatory responses and boost protein production. Their discovery enabled the development of mRNA-based vaccines for COVID-19, HIV, and other conditions (see Table 1, pages 5/6). In 2023, Drs. Karikó and Weissman received the Nobel Prize for this discovery.[1]

Government funding was key to the discovery and development of mRNA vaccines. Over decades, billions from taxpayers in the European Union, the United Kingdom and the United States[2,3,4] supported basic science and pre-clinical trials of mRNA-based vaccines — for cancer, HIV, influenza, rabies, Zika and other uses. In addition to purchasing COVID-19 vaccines, taxpayers funded later-stage clinical trials, manufacturing, and reduced financial risks for developers through advance purchase guarantees.

Moderna's COVID-19 vaccine was co-developed with the United States (US) National Institutes of Health. Although Pfizer did not accept US government funding for developing its COVID-19 vaccine, its partner, BioNTech (who co-developed and commercialized the vaccine), received nearly €450 million from Germany's government. In addition, BioNTech used a pre-fusion protein, developed with US government funding, to produce the COVID-19 vaccine.[5,6]

Pricing for COVID-19 Vaccines

Despite their huge contributions to mRNA vaccine development, governments in the US and the European Union (EU) did not impose vaccine price controls or other access-related conditions.

Pharmaceutical companies demanded confidentiality for their COVID-19 vaccine costs and prices, but some of this information was eventually disclosed to the public. The estimated manufacturing cost for mRNA-based COVID-19 vaccines, per dose, is $ 1.18 to $2.85.[7] Moderna and Pfizer/BioNTech charged the EU $25.50 and $25.15 per dose, respectively; the US Government paid an average price of $20.69 per dose for mRNA-based COVID-19 vaccines.[8,9] In March 2023, Moderna increased its per dose price to the US government from approximately $15 - $26 to $130.[10] In 2023, Pfizer announced an increase in the price of its COVID-19 vaccine, from just over $20 per dose to $110 - $130 per dose.[11,12]

How Do mRNA-Based COVID-19 Vaccines Work?

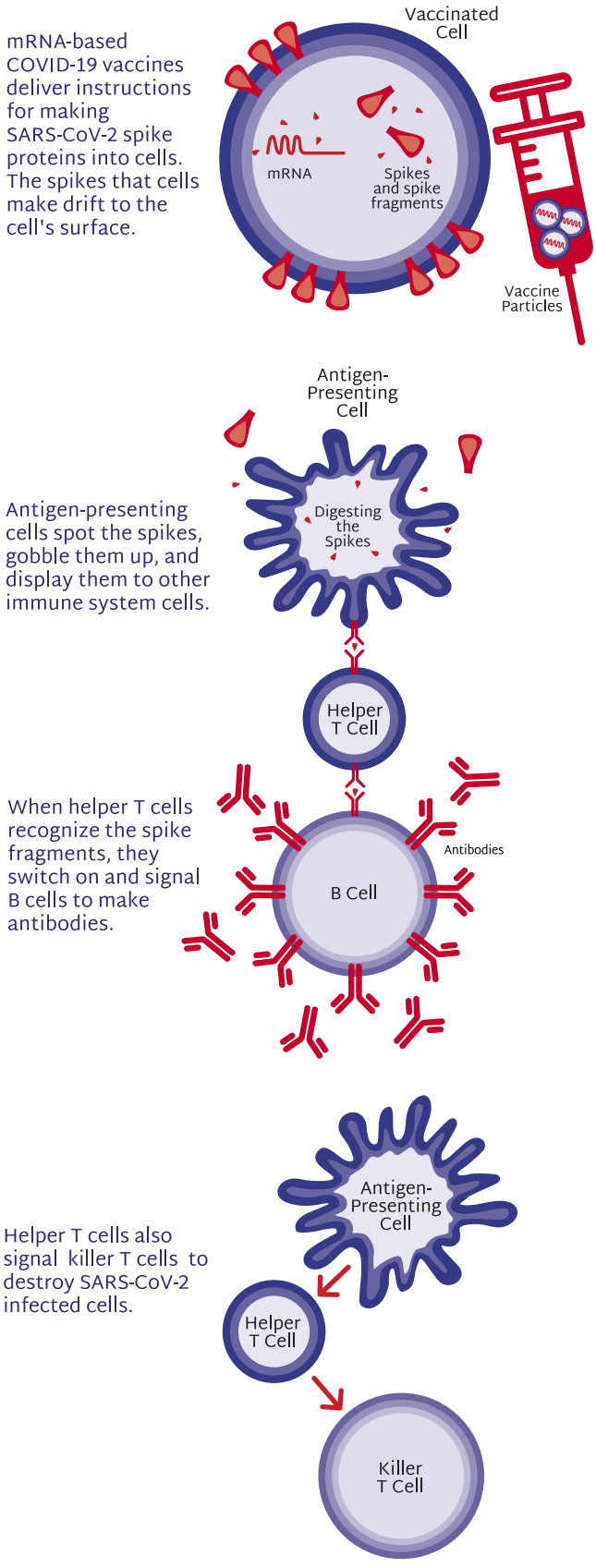
mRNA-based COVID-19 vaccines do the same thing as other vaccines: they trigger both general, non-specific immune responses (called innate) and specific immune responses (called adaptive). But they go about it in a different way than other vaccines, which train the immune system to respond to a weakened virus, a whole, deactivated virus, or parts of a virus (such as the SARS-CoV-2 spike protein). Instead, mRNA-based COVID-19 vaccines deliver lipid nanoparticle-wrapped instructions for making SARS-CoV-2's spike protein.

The vaccine's mRNA is broken down by the body after delivering instructions to make spike proteins into cells. After cells produce the spike proteins, they drift or poke their way out to the cell's surface, where they are spotted by immune cells known as antigen-presenting cells (APCs), which patrol the body, looking for invaders. APCs sweep up the spikes, process them, and display fragments of the spikes on their surface – just as they do when they encounter the SARS-CoV-2 virus. When helper T cells recognize these spike fragments, they become activated, signaling other parts of the immune system, including B cells (to make antibodies) and killer T cells (to destroy SARS-CoV-2 infected cells, which prevents COVID-19 from worsening).

How Effective Are mRNA-Based COVID-19 Vaccines?

The Phase III clinical trials for mRNA-based vaccines reported that they were up to 95% effective at preventing symptomatic COVID-19 within weeks of the second dose.[13,14] But things have changed since 2020, when these trials were performed:

- Unlike today, tests for COVID-19 were in short supply while trials were underway; only participants with certain symptoms were tested for SARS-CoV-2. But 45% of people who have COVID-19 are asymptomatic,[15] so it is likely that the number of infections occurring during trials were undercounted.
- The trials followed people for a short time – usually only a couple of months, making it difficult to estimate the durability of protection.



Adapted from: https://www.nytimes.com/interactive/2020/health/moderna-covid-19-vaccine.html

- The virus has changed since 2020. Until recently, all COVID-19 vaccines were based on the original virus, called the Wuhan strain. But SARS-CoV-2 has mutated many times since then, and several of its variants are better able to evade immune responses than the Wuhan strain. New booster doses have been adapted to members of the Omicron family, BA.4 and BA.5, and will continue to be updated.

Currently, it does not appear that any of the COVID-19 vaccines provide long-lasting protection against infection, because antibodies wane over time, usually within six months – and sometimes they do not recognize or respond to newer forms of the virus. Vaccine-induced T cell responses to SARS-CoV-2, which kill infected cells, are longer-lived than antibody responses;[16] because of these T cell responses, COVID-19 vaccines have proven to be better at preventing serious illness, hospitalization, and death from COVID-19 than preventing infection.

Advantages of the mRNA Platform

The mRNA platform has several advantages over traditional vaccine production methods. mRNA-based vaccines can be manufactured quickly. They are not cell-based, and do not rely on less predictable and potentially infectious agents. Instead, mRNA-based vaccines are produced from a stable chemical process, making them simpler, less expensive and faster to manufacture—taking weeks, rather than months. Producing mRNA vaccines requires less space and equipment than cell-based vaccines, so they can be manufactured in smaller facilities. Existing facilities can be used to produce mRNA-based vaccines and they can be rapidly updated or adapted to new pathogens. For example, Moderna's COVID-19 vaccine was designed just two days after the SARS-CoV-2 genome was published.[17] (Nonetheless, clinical trials will be needed for each new candidate).

The World Health Organization (WHO), in collaboration with the Medicines Patent Pool (MPP) and the COVAX ACT-Accelerator, created and oversees the mRNA vaccine technology transfer hub. The hub aims to increase capacity for producing mRNA-based vaccines in low and middle-income countries (LMIC). Co-leadership of LMIC vaccine producers is important to the success of this initiative. But key issues, such as the multiple patents on mRNA vaccines and some of their ingredients, must be resolved to enable widespread access to this important technology platform. For more details on local vaccine production and issues around vaccine access, visit our other briefs in this series, avac.org/FromLabToJab.

Concerns About mRNA-Based Vaccines

Many people were concerned about the speed at which mRNA-based vaccines were approved. But regulatory safeguards were already in place for assessing safety, efficacy and quality of medical products during health emergencies.[18] These safeguards include oversight of clinical trials, follow-up of study participants and compliance with good manufacturing practices. These controls are included in the requirements for Emergency Use Authorization (EUA), which is granted by national regulatory authorities, and WHO Emergency Use Listing (EUL).

The safety of mRNA vaccines is supported by the number of people who have received them. As of the end of Q1, 2023, nearly 2.9 billion of the 13.34 billion doses of COVID-19 vaccines administered globally[19] were mRNA-based (data from Argentina, Canada, Chile, Ecuador, Hong Kong, Japan, Nepal, Peru, South Africa, the EU, the US and Uruguay).[20] The benefits of mRNA-based COVID-19 vaccines have outweighed their risk; data modeling has estimated that, worldwide, these vaccines saved 19.8 million lives in just one year,[21] and the US Centers for Disease Control (CDC) reported that two or three doses of an mRNA-based COVID-19 vaccine lowered the risk of being put on a ventilator or dying by 90%.[22]

Adverse Events (AE) Associated with mRNA-based COVID-19 Vaccines

Many of the AE associated with mRNA-based vaccines – and other vaccines – are caused by immune responses. Vaccines trigger innate (and adaptive) immune responses. Innate responses are the body's first defense against infections; they can produce fever, joint and muscle pain, upset stomach, redness, swelling and pain at the injection site.

Most of the AE reported in clinical trials of mRNA vaccines (swelling, pain and/or redness at the injection site, fatigue, headache, muscle pain, fever, chills, joint pain, nausea and vomiting) have been mild and short-term. Some people may have felt too ill to return to work after getting vaccinated. They may not have been informed that their symptoms arose from their own immune responses to the vaccine (although vaccines are still effective for people who do not experience these AE).

mRNA-based vaccines (and other types of COVID-19 vaccines) are associated with myocarditis (an inflammation of the heart muscle) and pericarditis (an inflammation of the heart's outer lining), which are most common among male adolescents and young adults. Both are treatable and very rarely lead to death. The benefits of COVID-19 vaccines outweigh the cardiac risks; the risk of myocarditis from COVID-19 is seven times greater than from receiving an mRNA-based COVID-19 vaccine.[23]

Remaining Questions About mRNA Vaccines

There are several questions about mRNA-based vaccines, including:

- Whether they will be as, or more, effective than existing vaccines.
- Whether they will be effective for all new uses.
  - Data from a Phase IIb trial of a personalized mRNA-based cancer vaccine are promising, leading regulators in the EU and the US to expedite its development.
- Whether more than one dose of an mRNA vaccine will be required for current single-dose regimens.
- Whether the durability of protection from mRNA-based vaccines will be similar to other vaccines.
- Whether mRNA-based vaccine-induced adverse reactions will be more severe than those from existing vaccines, which could dissuade people from getting vaccinated.
- Whether cold chain requirements for transportation and storage can be modified.
- Whether materials for mRNA vaccines can be affordable and locally sourced.
- Whether LMICs hosting trials of mRNA-based vaccines will have access to these vaccines at an affordable price.
- What the impact of patents and other barriers will have on access to mRNA-based vaccines in LMIC.

Other mRNA Vaccines in Development

mRNA technology is currently being studied for many different uses.

Table 1, mRNA Candidates in Development*

Indication	Number of Candidates and Development Phase
Cancer (multiple types and stages); includes immunooncology and personalized vaccines, and with chemotherapy	31 (Phase I) 2 (Phase I/II) 4 (Phase II)
Congestive heart failure	1 (Phase I)
CMV	1 (Phase III)
Epstein-Barr Virus (to prevent mononucleosis)	1 (Phase I)
G6Pase Glycogen Storage Disease Type 1a (GSD1a)	1 (Phase I)
HIV	3 (Phase I)
HSV-2	1 (Phase I)
Influenza (monovalent and quadrivalent)	5 (Phase I) 5 (Phase I/II) 3 (Phase III)
Malaria	1 (Phase I)
Methylmalonic Acidemia	1 (Phase I/II)
Myocardial ischemia	1 (Phase II)
Nipah Virus	1 (Phase I)
PCCA/PCCB Propionic acidemia (PA)	1 (Phase II)
RSV (pediatric)	1 (Phase I)
RSV (older adults)	1 (Phase III)
SARS-CoV-2	4 (Phase I) 7 (Phase II) 5 (Phase III)
Shingles	1 (Phase I/II)
TB	2 (Phase I)
Zika Virus	1 (Phase II)
Combination vaccines	
Influenza/RSV	1 (Phase I)
Influenza/SARS-CoV-2	1 (Phase I) 1 (Phase I/II)
Influenza/ RSV/SARS-CoV-2	1 (Phase I)
Pediatric influenza/ pneumonia	1 (Phase I)

What Can Advocates Do?

JOIN OR INITIATE CAMPAIGNS to raise awareness of the need for local vaccine production and generate support for investment.

DEFINE and **INSIST** on government roles and responsibilities for the vaccines they fund, such as imposing price controls and requirements for access in places where research is conducted—for its participants, for additional research, and in LMIC.

PROMOTE research that assesses safety, effectiveness, durability of protection and adverse reactions of mRNA vaccines compared to vaccines from other platforms.

WORK with national health authorities to select vaccines (mRNA and other platforms if they are more effective) that are best for their country context.

CREATE and **SHARE** accurate information clearly, in local languages, to dispel misinformation about mRNA-based vaccines, and reduce vaccine hesitancy.

SUPPORT the mRNA vaccine technology transfer hub and other initiatives to increase production of mRNA-based vaccines in LMIC and ensure equitable access to them.

Resources

- **AVAC**. *Phase 1 mRNA HIV Vaccine Trials*, a snapshot of current HIV mRNA trials, and a primer on the basics of mRNA technology.
- **AVAC**. *What's All the Buzz About: mRNA, manufacturing, vaccine access*. This webinar explored how local manufacturing and the new mRNA Hub in South Africa could facilitate access and support R&D. Check out the summary, slides and recording.
- **CDC**. How mRNA Vaccines Work. https://www.cdc.gov/coronavirus/2019-ncov/downloads/vaccines/COVID-19-mRNA-infographic_G_508.pdf.
- **Public Citizen**. How To Make Enough Vaccine for the World in One Year: https://www.citizen.org/article/how-to-make-enough-vaccine-for-the-world-in-one-year/.
- Speaking of Research – information on the development of mRNA vaccines: https://speakingofresearch.com/2021/08/27/human-mrna-vaccine-trials-in-the-2010s-a-history-lesson-in-animal-research/.
- **WHO**.The mRNA vaccine technology transfer hub. https://www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub.

Footnotes

[1] https://www.nobelprize.org/prizes/medicine/2023/press-release/
[2] https://www.bmj.com/content/380/bmj-2022-073747
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[16] https://www.nature.com/articles/s41590-022-01175-5
[17] https://www.businessinsider.com/moderna-designed-coronavirus-vaccine-in-2-days-2020-11
[18] See: www.avac.org/resource/regulatory-approval-primer-vaccine-advocates
[19] https://ourworldindata.org/covid-vaccinations
[20] https://ourworldindata.org/grapher/covid-vaccine-doses-by-manufacturer?country=~URY
[21] https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00320-6/fulltext
[22] https://www.cdc.gov/mmwr/volumes/71/wr/mm7112e1.htm
[23] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9467278/

About This Brief

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About AVAC

AVAC is an international non-profit organization that leverages its independent voice and global partnerships to accelerate ethical development and equitable delivery of effective HIV prevention options, as part of a comprehensive and integrated pathway to global health equity. Follow AVAC on Twitter @HIVpxresearch; find more at www.avac.org, www.prepwatch.org and www.stiwatch.org.